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REVIEW

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# The Beneficial Role of Thiamine in Parkinson Disease

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## SUMMARY

Parkinson disease (PD) is the second most common form of neurodegeneration among elderly individuals. PD is clinically characterized by tremors, rigidity, slowness of movement, and postural imbalance. In this paper, we review the evidence for an association between PD and thiamine. Interestingly, a significant association has been demonstrated between PD and low levels of serum thiamine, and thiamine supplements appear to have beneficial clinical effects against PD. Multiple studies have evaluated the connection between thiamine and PD pathology, and candidate pathways involve the transcription factor Sp1, p53, Bcl-2, caspase-3, tyrosine hydroxylase, glycogen synthase kinase-3$\beta$, vascular endothelial growth factor, advanced glycation end products, nuclear factor kappa B, mitogen-activated protein kinase, and the reduced form of nicotinamide adenine dinucleotide phosphate. Thus, a review of the literature suggests that thiamine plays a role in PD, although further investigation into the effects of thiamine in PD is needed.

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## Introduction

Parkinson disease (PD) is a movement disorder that is characterized by tremor, rigidity, akinesia, and loss of posture reflexes, which often leads to immobility and frequent falls. PD results from the selective loss of dopaminergic (DA) neurons in the substantia nigra (SN) of the brain. Studies have suggested a relationship between dopamine and thiamine, dopamine has been shown to suppress the mouse-killing aggression (muricide) induced by a thiamine-deficient (TD) diet [1], and this suppressive effect can be potentiated by carbidopa [2]. Patients with PD who have undergone levodopa (L-dopa) therapy show significantly higher cerebrospinal fluid (CSF) levels of thiamine diphosphate (TDP) and total thiamine than do patients who are not treated with this drug [3]. Moreover, thiamine deficiency can decrease the concentration of dopamine in the striatum, whereas animals that are fed a diet containing 5% ethanol show increased dopamine turnover [4]. In an animal experimental study of thiamine deficiency, region-specific vesicular dysfunction, that is, a decreased level of dopamine metabolite, was observed posttreatment [5]. Intrastriatal administration of thiamin triphosphate (TTP) or TDP has been shown to induce dopamine release [6], and thiamine derivatives are known to be present in high concentrations in the human SN [7]. Dopamine release can be induced by the intrastriatal administration of TPP or TDP, reaching levels that are as high as 1400% and 249% of the basal levels, respectively, whereas reduced levels of dopamine in the striatum can occur in thiamine deficiency [6]. Furthermore, decreased CSF-free thiamine levels were noted in patients with PD as compared to controls [3]. In parkinsonism-dementia patients, thiamine pyrophosphatase activity was found to be significantly reduced in the frontal cortex [8]. In addition, Gold et al. [9] reported that 70% and 33% of their patients with PD had low plasma thiamine and low RBC thiamine levels, respectively. Starvation-induced TD encephalopathy may also cause symmetrical lesions in the SN [10]. Together, these findings suggest that thiamine may play a role in DA neuron activity. Interestingly, parental thiamine administration was used successfully in 9 nonalcoholic patients who presented with acute neurological disorders [11]. In addition, the administration of a combination of thiamine and acetazolamide was reported to reduce scores on the Abnormal Involuntary Movement Scale (AIMS) and the Simpson–Angus Neurological Rating Scale (ANRS) in patients with tardive dyskinesia and parkinsonism symptoms [12]. Recently, thiamine has been shown to also improve the symptoms associated with PD; within days of thiamine treatment, patients reportedly had smiles on their faces, walked normally with longer strides, increased their arm swings, and experienced no tremors or sialorrhea. In addition, 3 patients no longer required carbidopa or levodopa and did not suffer ill effects on their movements. [13]. In a previous publication, we identified a number of proteins that link thiamine to PD pathology [14]. In the present paper, we will further discuss the relationship between thiamine and PD.

## The Role of Thiamine in Parkinson Disease

The Sp1 transcription factor is a member of an extended family of DNA-binding proteins that are acetylated in neurons in response to oxidative stress [15]. The Sp1 family of proteins plays an important role in controlling the expression of the dopamine transporter gene within DA neurons [16], and these proteins also regulate the expression of the rat dopamine receptor gene [17]. The rat dopamine receptor contains multiple Sp1-binding sites [17,18]. Sp1 or another protein antigenitically related to Sp1 is included in the complex that binds the activator region of the human $D_{1A}$ dopamine receptor gene [19]. A novel 130-kDa factor recognizing Sp1-binding sequences in the $D_2$ gene negative modulator is also found in nuclear extract from the rat striatum [20]. Furthermore, the human monoamine oxidase (MAO) B plays a major role in the degradation of biogenic and dietary amines such as phenylethylamine, benzylamine, dopamine, and tyramine. The human monoamine oxidase B gene was also regulated by Sp1 and Sp3 [21]. Similarly, thiamine uptake in the human intestine occurs via a specialized carrier-mediated mechanism, and the human thiamine transporters (THTRs) are expressed in the intestine and are regulated via *Sp1* promoter elements [22,23]. These findings suggest a link between thiamine, Sp1, and DA transporter and indicate that the *Sp1* family of proteins plays an important role in controlling the expression of the dopamine transporter gene within DA neurons and also regulates the activity of *SLC19A3* gene in transport thiamine.

The p53 gene and protein play critical roles in regulation of the normal cell cycle, cell cycle arrest, and the apoptotic response. p53 is a transcription factor that plays a major role in determining cell fates in response to DNA damage; in the central nervous system (CNS), the function of p53 is to serve as a critical regulator of neuronal cell apoptosis [24]. Specifically, p53 is involved in the dopamine-induced apoptosis of cellular granule neurons [25]. In p53-knockout mice, DA neurons were shown to be more resistant to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity than normal neurons [26], and an increase in p53 expression was observed in autopsied tissue from patients with PD [27,28]. Furthermore, levels of p53 immunoreactivity increased following 6-hydroxydopamine (6-OHDA)-induced apoptosis of nigral dopaminergic neurons [29]. The activation of p53 has been reported in animal models of PD, and inhibition of p53 activity was shown to prevent MPTP-induced degeneration of DA neurons [30]. These findings suggest that p53-associated apoptosis may be a common mechanism of cell loss in several important neurodegenerative diseases. In addition, the presence of abundant p53-immunoreactive neurites and glial cell processes appears to be a novel feature of neurodegeneration shared by these distinct diseases. Parkin is a PD-associated gene that contributes to the functions of p53 [31]. Genetic depletion of endogenous parkin increases the expression, activity, and mRNA levels of p53 [32]. Moreover, an increased number of thiamine transporters has been observed in cells that over-express thiamine transport genes (mTHTR-1) and in cells exposed to conditions that induce DNA damage or p53 activation [33]. TDP inhibits p53 binding, whereas thiamine inhibits intracellular p53 activity [34]. In addition, the expression of p53 is significantly decreased when cultures of retinal neurons from diabetic rats are treated with thiamine [35]. These observations suggest that the transcription factor p53 is activated in PD, which increases the apoptotic response to cellular damage, and that thiamine ameliorates the cellular effects of activated p53.

Bcl-2 is a membrane-bound protein that plays a neuroprotective role in the CNS. Bcl-2 inhibits apoptosis and enhances the survival of newly formed neurons in the normal and ischemic hippocampus [36], and Bcl-2 mRNA and protein expression are developmentally regulated in both the human and murine brains [37,38]. Bcl-2 was shown to inhibit cell death caused by serum and growth-factor withdrawal in a central neural cell line, and it has also been shown to have inhibitory effects on calcium ionophore A23187, glucose withdrawal, membrane peroxidation, and, in some cases, even free-radical-induced damage [39]. Oxidative stress induced by the neurotoxins MPTP, paraquat, maneb, and rotenone causes lipid peroxidation and protein misfolding, which has effects on cell death through members of the Bcl-2 family [40]. MPTP-induced DA neuron toxicity was shown to decrease the expression of Bcl-2 in mouse SN [41], whereas Bcl-2 overexpression was protective against MPTP toxicity [41,42] and 6-OHDA toxicity [43,44]. Interestingly, high cellular concentrations of α-synuclein have been shown to downregulate Bcl-2 expression [45]. G-protein-coupled receptor kinase 9 (GRK5) has been reported to accumulate in Lewy bodies, which are over-expressed in the α-synuclein model of PD, and regulate Bcl-2 expression [46]. In addition, glial cell-line-derived neurotrophic factor promoted the survival of grafted midbrain-derived neural stem cells and increases the expression of Bcl-2 in a rat model of PD [47]. The endoplasmic reticulum (ER) chaperone $\sigma$-1 receptor (Sig-1R) is cytoprotective against ER stress-induced apoptosis [48], and Sig-1Rs are downregulated in the brains of patients with early stage PD [49]. Dopamine was shown to induce apoptosis in Sig-1R knockdown Chinese Hamster ovary cells, which could be blocked by the over-expression of Bcl-2 [50]. Therefore, decreased Bcl-2 protein levels suggest increased levels of apoptosis in patients with PD. However, pretreatment with B vitamins ($B_1$, $B_6$, and $B_{12}$) had a protective effect on experimentally induced epilepsy of the mouse brain, which was associated with the induction of Bcl-2 expression within 12 h of treatment [51]. Moreover, thiamine deprivation was shown to increase cell death and reduce Bcl-2 expression during hybridoma cell culture [52]. Benfotiamine improves the functional recovery of infarcted hearts and increases Bcl-2 protein levels [53], and it was also shown to prevent LPS-induced apoptosis and enhance Bcl-2 expression in a mouse macrophage cell line [54]. Furthermore, when human and bovine pericytes were intermittently exposed to high levels of glucose, there was a 50–60% decrease in the Bcl-2-to-Bax expression ratio, and the addition of thiamine and benfotiamine completely reversed this damaging effect [55]. Altogether, these results suggest that thiamine may have a neuroprotective role in PD by increasing expression of the apoptotic inhibitor Bcl-2.

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis [56]. Activation of caspases and the apoptosis of DA neurons have been implicated in the pathogenesis of PD. Activated caspases-3

 

has been observed in the SN of patients with PD [57,58], and intranigral lipopolysaccharide (LPS) injection was shown to induce the degeneration of DA neurons and increases caspase-3 activation in the rat ventral mesencephalon [59]. Glial-cell-line-derived neurotrophic factors were shown to promote the survival of grafted midbrain-derived neural stem cells, and reduce the expression of caspase-3 in a rat model of PD [47]. Moreover, caspase-3 inhibitors were shown to protect neuronal cells from MPTP-induced apoptosis [60], and gene disruption of caspase-3 prevented MPTP-induced apoptosis in the SN [61]. These findings suggest that caspase-3 activation precedes and is not a consequence of apoptotic cell death in PD. However, thiamine transporter *SLC19A3* gene-transfected breast cancer cells also demonstrated increased levels of apoptosis when exposed to doxorubicin and radiation, and this effect was partially mediated by a caspase-3-dependent pathway [62]. Furthermore, the thiamine deficiency caused by thiamine antagonists was shown to lead to caspase-3-dependent apoptosis in neuronally differentiated rat PC-12 cells [63]. In addition, benfotiamine accelerated the healing of ischemic diabetic limbs in mice via the potentiation of angiogenesis and prevented the induction of pro-apoptotic caspase-3 [64], and this compound was also shown to prevent LPS-induced apoptosis and caspase activation in a mouse macrophage cell line [54]. In addition, sulbutiamine, a highly lipid-soluble synthetic analog of thiamine, was shown to attenuate trophic-factor-deprivation-induced cell death in transformed retinal ganglion cells (RGC-5) and decreases the expression of cleaved caspase-3 [65]. These findings suggest that thiamine may play a role in PD by inhibiting the activity of the apoptotic factor caspase-3.

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the biosynthesis of dopamine and other catecholamines. In normal human brains, the mRNA levels of human $TH_{1\text{-}2}$ are much greater than those of human $TH_{3\text{-}4}$. Marked and parallel decreases in mRNA levels of human $TH_{1\text{-}4}$ are found in the SN in PD [66]. Humans and monkeys, having multiple TH isoforms, are more susceptible to MPTP than nonprimate mammals with a single form such as mice and rats, which have low susceptibility to MPTP. Such a difference may suggest the functional significance of TH isoforms in PD. The activity and protein level of TH are decreased to cause DA deficiency in the striatum in PD. However, the homo-specific activity (activity/enzyme protein) of TH is increased. This increase in TH homo-specific activity suggests activation by increased phosphorylation at the N-terminus of the TH protein for a compensatory increase in DA synthesis. This compensatory activation of TH by phosphorylation in the remaining DA neurons may contribute to a further decrease in TH protein and activity in DA neurons in PD, causing a vicious circle of decreasing TH activity, protein level, and DA contents [67]. mRNA level and protein content of TH are markedly decreased in the SN and striatum of the postmortem PD brain [68]. The pathophysiology of PD is largely due to the nigro-striatal DA system, as decreases in TH activity, TH synthesis, and TH mRNA levels in the striatum of patients with PD and PD animal models have been observed [69,70]. During the treatment with chronic low dose MPTP, mice developed dopamine-dependent movement deficits induced by loss of TH-positive nigrostriatal axon terminals [71]. MPTP-treated cats exhibited severe Parkinson-like motor syndrome during the acute period with a marked decrease in TH-immunoreactivity in the striatum [72]. The gait variability in the PD mice showed a closer correlation with the protein levels of TH in the SN than the walking distances in the conventional open field test [73]. The L-dopa-induced increase in striatal TH-immunoreactive neurons is dose dependent and persists for days after L-dopa withdrawal [74]. In addition, TH gene mutations have been reported to be associated with PD; a TH heterozygous variant was reported in one patient with dopa-responsive dystonia simulating spastic paraplegia [75] as well as in early-onset patients with PD [76]. In addition, a novel deletion in the TH gene was detected in one patients with PD [77], and decreased levels of TH protein were noted in the striatum of the MPTP-induced neurotoxic lesions of animals with experimental PD [78]. Moreover, the fluorescence intensity of TH expression was decreased in the limbic cortex and brainstem in TD mice compared with pair-fed mice as the control group [79]. In addition, male Wistar rats maintained on a TD diet demonstrated mouse-killing behavior, which was attenuated by the administration of L-dopa [80]. Similarly, this suppressive effect was shown to be potentiated by carbidopa [2].

Glycogen synthase kinase-3$\beta$ (GSK3$\beta$) is a protein kinase that is involved in many physiological processes (e.g., metabolism, gene expression, and apoptosis). GSK3$\beta$ is pivotal in controlling neuronal polarity within primary embryonic hippocampal neurons [81]. GSK3$\beta$ is associated with the fate of DA neurons in PD and may exert its toxicity via the induction of apoptosis by the direct activation of intrinsic cascades or via the phosphorylation of synphilin-1 or $\alpha$-synuclein. GSK3$\beta$ expression is increased in brain regions associated with PD pathology [82]. In animal and cell culture models of PD, rotenone-induced cytotoxicity is mediated by microtubule destabilization via GSK3$\beta$ activation, and that microtubule destabilization is caused by reduction in the binding capacity of tau to microtubules, which is a result of tau phosphorylation via GSK3$\beta$ activation. Rotenone-induced cytotoxicity in SH-SY5Y cells was attenuated by the GSK3$\beta$ inhibitor SB216763 [83]. GSK3$\beta$ polymorphisms alter transcription and splicing by interacting with Tau haplotypes to modify disease risk in patients with PD [84]. Haplotype analysis revealed that the *TT* haplotype of GSK3$\beta$ polymorphisms was over-represented in patients with PD as compared to controls [85]. However, GSK3$\beta$ variant reduces the risk of PD in Han Chinese population [86]. The GSK3 inhibitor reduces L-dopa-induced neurotoxicity [87], and exposure to pyrithiamine, an antithiamine compound, increases A$\beta$ accumulation and GSK3 activity in the brain [88]. In an animal model of AD, benfotiamine was shown to improve cognitive function, reduce amyloid deposition, and suppress GSK3 activity [89]. These findings suggest that thiamine may play a role in PD by suppressing GSK3 activity.

Angiogenesis is a complex process that involves coordinated endothelial cell activation, proliferation, migration, tube formation, and capillary sprouting In addition, angiogenesis requires the participation of numerous intracellular signaling pathways. Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and has been shown to have neuroprotective effects on DA neurons in models of 6-OHDA-induced toxicity, to decrease amphetamine-induced rotational behavior, and to preserve TH-positive neurons and fibers [90]. In rat midbrain cultures, increased levels of VEGF-B transcription have been reported following the addition of the neurotoxin rotenone [91], suggesting that the growth factor VEGF-B can improve neuronal survival in a

culture model of PD. An increase in the number of VEGF-positive neurons and blood vessels was also been demonstrated in the SN of mice with MPTP-induced neurotoxicity [92]. These changes in vascularization may therefore modify the neuronal availability of blood nutrients, blood cells or toxic substances, and neuronal susceptibility to parkinsonism. Wada et al. [93] further demonstrated upregulated expression of VEGF in the SN of patients with PD. In PD animal models, the neuroprotective effects of VEGF appear to be dose dependent. Indeed, low doses of VEGF have been shown to have a neuroprotective effect on DA neurons and have been shown to result in behavioral improvement, whereas high doses have been shown to induce angiogenesis and glial proliferation [94]. Moreover, thiamine deficiency was shown to result in polyneuropathy after gastrectomy, and this deficiency has also been associated with high levels of serum VEGF, which typically returned to normal following the intravenous administration of thiamine, which further improves symptoms of polyneuropathy [95]. In addition, increased serum levels of VEGF have been reported in patients with wet beriberi [96]. In a model of peritoneal dialysis in uremic rats, treatment with benfotiamine decreased peritoneal fibrosis, markers of inflammation, neovascularization, and VEGF staining [97]. Furthermore, benfotiamine was also shown to improve the functional recovery of infarcted hearts and also reduce the phosphorylation/activation of VEGF receptor 2/Akt signaling pathways in a mouse macrophage cell line [53].

Glyoxalase 1 (Glyo-1) catalyzes the initial rate-limiting step in the removal of methylglyoxal (MG), which is the major precursor for advanced glycation end products (AGEs). AGEs represent a heterogeneous group of macromolecules that are formed by the nonenzymatic glycation of proteins, lipids, and nucleic acids. RAGEs are multiligand receptors, and their ligands also likely recognize several receptors to mediate their numerous biological effects [98]. α-Synuclein has been implicated in PD, and its deficiency leads to increased Glyo-1 expression and glycation stress [99]. Altered Glyo-1 expression was also reported in brain of mouse with parkin deficiency [100]. Furthermore, glycation was observed in the SN and locus ceruleus, with the greatest levels of immunoreactivity at the periphery of Lewy bodies, in patients with PD [101]. In addition, AGEs were shown to stimulate the *in vitro* cross-linking of α-synuclein and accelerate intracellular inclusion body formation [102], and RAGE levels were found to be over-expressed in patients with PD as compared to age-matched controls [103]. RAGE deficiency protects nigral DA neurons against cell death induced by the neurotoxin MPTP, and this type of cell death mimics many of the characteristic features of PD [104]. Moreover, thiamine and benfotiamine supplementation prevented the tissue accumulation and increased the urinary excretion of protein glycation, oxidation, and nitration adducts associated with experimental diabetes [105]. Karachalias et al. [106] reported that the hydroimidazolone of AGE residues derived from glyoxal and methylglyoxal (G-H1 and MG-H1) was increased by 115% and 68%, respectively, in streptozotocin-induced diabetic rats, whereas treatment with thiamine and benfotiamine normalized these effects. However, N-carboxymethyl-lysine (CML) and N-carboxyethyl-lysine (CEL) residues increased by 74% and 118%, respectively, in diabetic-induced rats, and only treatment with thiamine normalized these effects. In addition, serum markers of endothelial dysfunction, oxidative stress, and AGEs were shown to be increased following a meal high in AGE content, although benfotiamine significantly reduced these effects [107]. The addition of benfotiamine was also shown to enhance transketolase activity and decrease the expression of AGEs and RAGEs in a model of peritoneal dialysis in uremic rats [97]. In both bovine aortic endothelial cells and the retinas of diabetic rats, benfotiamine inhibited the AGE formation pathway by activating transketolase and prevented experimental diabetic retinopathy [108]. Furthermore, the combined administration of thiamine and vitamin B6 to patients with diabetic nephropathy decreased DNA glycation in leukocytes, although vitamin B6 alone did not have such an effect [109].

The transcription factor nuclear factor kappa B (NF-κB) is a hetero-dimeric, sequence-specific transcription factor that is found in many cell types. NF-κB has been implicated in chronic inflammatory diseases, and it is a key regulator of genes involved in responses to infection, inflammation, and stress. Increased activation of NF-κB has been reported in DA neurons of the SN in patients with PD as compared to controls [28,110,111]. NF-κB has also been identified as a component of Lewy bodies [112]. A significant increase in NF-κB was observed mainly in glial cells of the SN during MPTP-induced apoptosis in a mouse model of PD [113]. Furthermore, α-synuclein over-expression was shown to enhance manganese-induced neurotoxicity via the NF-κB-mediated pathway [114]. Selective inhibition of NF-κB activation was shown to suppress nigral microglial activation and improve motor function in a mouse model of PD [115], and benfotiamine was also shown to inhibit NF-κB activation, via the activation of transketolase, and prevent experimental diabetic retinopathy in both bovine aortic endothelial cells and the retinas of diabetic rats [108]. Benfotiamine was further shown to prevent endotoxin-induced inflammation by suppressing oxidative-stress-induced NF-κB activation in rats with endotoxin-induced uveitis and in murine macrophage cell lines [54,116], and benfotiamine-mediated suppression of expression of NF-κB prevented LPS-induced macrophage cell death and monocyte adhesion to endothelial cells [117]. Altogether, these findings indicate that thiamine may suppress NF-κB activation in PD.

The mitogen-activated protein kinase (MAPK) pathways provide a key link between membrane-bound receptors and changes in gene expression, involving the extracellular signal-regulated kinase (ERK) cascade, the stress-activated protein kinases/c-jun N-terminal kinase (SAPK/JNK) cascade, and the p38 MAPK/RK/HOG cascade [118]. Increased cytoplasmic ERK1/2 activity has been observed in the brains of human patients with PD [119], and degenerating SN neurons typically display phosphorylated-ERK1/2 granules [120]. The activation of ERK1/2 is induced by the neurotoxin 6-OHDA, and inhibition of ERK activation enhances neuronal survival [121,122]. The mitochondrial localization of ERK2 activity suggests an effect of 6-OHDA on mitophagy and autophagic cell death in PD [123]. Dysregulation of the autophagy pathway has been observed in the brains of patients with PD and in animal models of PD [124,125]. In addition, the activation of p38 MAPK has been demonstrated in the SN of MPTP-treated mouse models of PD [126]. Moreover, vulnerability to glutamate-induced toxicity in DA neurons is dependent on endogenous dopamine

 

as well as MAPK activation [126]. Interestingly, genetic deficiency in MAPK kinase $2^{-/-}$ prevented MPTP-induced neurotoxicity in mouse models of PD [127]. Moreover, benfotiamine was shown to modulate the macrophage response to bacterial endotoxin-induced inflammation by preventing the activation of p-38 MAPK and stress-activated kinases (SAPK/JNK) [54].

The reduced form of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme complex mediates critical physiological and pathological processes including cell signaling, inflammation, and mitogenesis, by generating reactive oxygen species (ROS) from molecular oxygen. NOX is widely expressed in various immune cells, including microglia, macrophages, and neutrophils. NOX expression was observed in the nuclei of DA neurons in the SN of patients with PD and animals with 6-OHDA-induced neurotoxicity [128]. NOX activation was reported to increase zinc-induced DA neurodegeneration as well as MPPT, rotenone, angiotensin, and paraquat-induced neurotoxicity in animal models of PD [129–133]. Inhibition and knockdown of NOX were shown to reduce paraquat-induced ROS generation and DA cell death [133], and NOX inhibitors were also shown to protect against LPS-induced toxicity, MPPT-induced oxidative stress, and apoptosis in mesencephalic DA neuronal cells [134,135]. Thiamine is an essential coenzyme for transketolase, which is part of the pentose phosphate pathway that helps maintain cellular NADPH levels. In a study that administered glyoxal toxicity to hepatocytes, thiamin demonstrated cytoprotective functions and restored NADPH levels, glyoxal detoxification, and mitochondrial membrane potential [136]. Furthermore, NADPH-cytochrome c reductase levels were increased in TD animals [137], and benfotiamine treatment under both normo- and hyper-glycemic conditions significantly downregulated Nox4 expression [138]. In addition, animals that were fed a high-thiamine diet had approximately 57% of the NADPH-cytochrome c reductase activity of those that were fed a TD diet [139]. Altogether, these results suggest that thiamine may be neuroprotective against PD by regulating NADPH-cytochrome c activity.

## Conclusions

Thiamine plays a beneficial role in PD by inducing dopamine release and improving the symptoms associated with PD. Genetic studies have provided the opportunity to identify the specific proteins that link thiamine to the pathology of PD. Thiamine also exerts its effects on PD via nongenomic mechanisms. In addition, thiamine involved in PD, including the DJ-1 gene, excitatory amino acid transporters (EAATs), the α-ketoglutarate dehydrogenase complex, coenzyme Q10, lipoamide dehydrogenase, chromosome 7, transcription factor p53, the renin–angiotensin system, heme oxygenase-1, and *poly(ADP-ribose) polymerase-1* gene [14]. However, gastrointestinal dysfunction is common in patients with PD, and it potentially affects the therapeutic intervention [140]. Gastric emptying has been reported to be frequently delayed in patients with PD [141]. Decreased nonmediated uptake across the enterocyte brush border membrane was demonstrated in patients with PD [142]. In addition, the intestinal absorption of thiamine is sufficient in young people but may be reduced with age [143]. Parental administration of thiamine may be suitable for patients with PD [14]. Thus, further studies are needed to determine the potential benefits of using thiamine as a treatment for PD.

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## Conflict of Interest

The authors declare no conflict of interest.

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